

(PCT Article 36 and Rule 70)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/FR2004/003397

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
- ☐ the international application as originally filed/furnished
- ☒ the description:
- pages 1-30 _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☒ the claims:
- nos. _____ as originally filed/furnished
- nos.* _____ as amended (together with any statement) under Article 19
- nos.* 1-18 _____ received by this Authority on 29.05.2006 with telefax
- nos.* _____ received by this Authority on _____
- ☐ the drawings:
- sheets _____ as originally filed/furnished
- sheets* _____ received by this Authority on _____
- sheets* _____ received by this Authority on _____
- ☒ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages _____
- ☒ the claims, nos. 19-21 _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1.	Statement		
	Novelty (N)	Claims <u>16, 17</u>	YES
		Claims <u>1-15, 18</u>	NO
	Inventive step (IS)	Claims _____	YES
		Claims <u>1-18</u>	NO
	Industrial applicability (IA)	Claims <u>1-18</u>	YES
		Claims _____	NO
2.	Citations and explanations (Rule 70.7)		
1.	Reference is made to the following documents:		
	D1: WO 95/02069 A (BENNETT C FRANK; BOGGS RUSSELL T (US); DEAN NICHOLAS M (US); ISIS PHA) 19 January 1995 (1995-01-19)		
	D2: PARK H-Y ET AL: "THE BETA ISOFORM OF PROTEIN KINASE C STIMULATES HUMAN MELANOGENESIS BY ACTIVATING TYROSINASE IN PIGMENT CELLS" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 268, no. 16, 5 June 1993 (1993-06-05), pages 11742-11749, XP002036373 ISSN: 0021-9258		
	D3: NISHIZUKA Y: "THE MOLECULAR HETEROGENEITY OF PROTEIN KINASE C AND ITS IMPLICATIONS FOR CELLULAR REGULATION" NATURE, NATURE PUBLISHING GROUP, LONDON, GB, vol. 334, 25 August 1988 (1988-08-25), pages 661-665, XP001118326 ISSN: 0028-0836		
	D4: PARK H-Y ET AL: "The receptor for activated C-kinase-1 (RACK-I) anchors activated PKC- β on melanosomes", J. of Cell Science, 117(16), July 2004, 3659-3668, published after the priority date and cited by the applicant.		
	D5: PARK H-Y ET AL: "Topical Application of a protein kinase C inhibitor reduces skin and hair		

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	<p>pigmentation", J. Invest Dermatol., 122:159-166, Jan. 2004, published after the priority date and cited by the applicant.</p> <p>2. Claims 1 to 15 and 18</p> <p>The present application fails to meet the requirements of PCT Article 33(1), since the subject matter of claims 1 to 15 and 18 does not comply with the criterion of novelty as defined by PCT Article 33(2). Moreover, the subject matter of said claims relates to a topical pharmaceutical composition including an oligonucleotide capable of hybridising specifically with PKC-beta-1 genes.</p> <p>D1 describes (see pages 25 to 26) antisense oligonucleotides enabling specific hybridisation with the genes or messenger RNA coding for the protein PKC-beta 1, so as to modulate the expression thereof, and, more particularly, oligonucleotides having sequences identical to those of the present claim 3 (see the table: SEQ.ID N°25 of D1 = SEQ.ID N°2; SEQ.ID N°26 of D1 = SEQ.ID N°3; SEQ.ID N°27 of D1 = SEQ.ID N°4; SEQ.ID N°28 of D1 = SEQ.ID N°1; SEQ.ID N°29 of D1 = SEQ.ID N°5). Said oligonucleotides can also be modified (see claims 3 to 13 of D1).</p> <p>Furthermore, D1 claims the pharmaceutical compositions containing said oligonucleotides (see claim 36) and more particularly the topical formulations (see page 18, lines 6 to 19).</p> <p>Hence, D1 entirely anticipates the subject matter of claims 1 to 15 and 18 of the present application.</p>

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	<p>However, the use of such oligonucleotides for preparing a topical pharmaceutical composition for treating or preventing regional hyperpigmentations caused by melanocyte hyperactivity, as claimed in the original claim 20 is to be considered novel over D1.</p> <p>3. Claims 16 to 17</p> <p>The oligonucleotides described in D1 are specific to the various isoforms of the protein PKC and enable the role of these various isozymes to be assessed, hence they can be used in the treatment of illnesses associated with these specific isozymes, such as inflammations and hyperproliferative disorders. However, D1 does not mention the specific role played in melanogenesis by the beta-1 isoform of the protein kinase C.</p> <p>The subject matter of claims 16 and 17, which relate respectively to cosmetic compositions containing the oligonucleotides according to claims 1 to 15 and the use thereof as an inhibitor of melanine synthesis for depigmenting or bleaching the skin or hair, is novel over D1.</p> <p>However, the present application fails to meet the requirements of PCT Article 33(1), since the subject matter of claims 16 and 17 does not involve an inventive step as defined by PCT Article 33(3).</p> <p>D2, which is considered to be the closest prior art, describes the role as an activator of tyrosinase by phosphorylation played by PKC and the key role of</p>

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	<p>tyrosinase in melanogenesis, and assesses the functions of each of the isoforms of PKC according to the cell types and explicitly indicates that skin pigmentation is directly associated with the beta isoform of the protein kinase C. D2 therefore explicitly describes the role of PKC-beta in melanogenesis (see abstract). Consequently, the subject matter of claims 16 and 17 of the present application differs from D2 only in that it refers to the beta 1 isoform of PKC and the specific role thereof in melanogenesis.</p> <p>Apart from the fact that D4 and D5 were published after the priority date of the present application, contrary to the applicant's assertions, specific inhibitors of the various isoforms of the protein kinase C are known from the prior art, particularly from D1. Furthermore, referring to D4, page 3660, left-hand column, fourth paragraph, the applicant is of the opinion that it follows therefrom that PKC $\beta 2$ is specifically involved in the stimulation of melanogenesis. However, according to D4, this information is derived ("<u>Therefore</u>, PKC-$\beta 2$ is specifically implicated in...") from transfection studies performed on human NP-melanocytes with cDNA of PKC-β<u>II</u> showing the activation of tyrosinase as described in the document "Park et al., 1993" (see D4, preceding sentence). According to the references of D4, said document "Park et al., 1993" is indeed D2, which, contrary to the assertions of D4, does not mention at any point the role played by the isoform βII as a tyrosinase activator in melanogenesis. D2 merely indicates the specific role of the beta isoform of PKC in melanogenesis, without investigating further types 1</p>

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	<p>and/or 2 of this isoform.</p> <p>At the priority date of the present application and in the light of D2, which is considered to be the closest prior art, the problem that the present invention is intended to solve can therefore be considered to be that of obtaining inhibitors of PKC β proteins, capable of blocking the activation of tyrosinase in melanogenesis, for depigmenting or bleaching the skin.</p> <p>The solution proposed in claims 16 and 17 of the present claim is not considered inventive (PCT Article 33(3)) for the following reasons;</p> <p>The various isoforms α, β_I, β_{II}, ζ, δ, γ and ϵ of PKC are known from the prior art (see for example D1 and D3) and the inhibitors thereof or even the specific antisense oligonucleotides of each of said isoforms, particularly beta and more particularly beta 1 or beta 2, are also known from D1 (see pages 26 to 27, tables 2 to 4) so as to modulate the specific expression of each of said genes.</p> <p>Thus, in the light of D1, it is obvious for a person skilled in the art seeking to solve the stated problem to apply these antisense oligonucleotides known from tables 2 to 4 of D1 in routine hybridisation studies so as to assess the inhibiting activity and the specificity of each of said beta isoforms in melanogenesis, as taught in D2, and thereby obtain the features according to claims 16 and 17 without exercising inventive skill.</p>

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
- a. type of material
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ in written format
- ☐ in computer readable form
- c. time of filing/furnishing
- ☒ contained in the international application as filed
- ☒ filed together with the international application in computer readable form
- ☐ furnished subsequently to this Authority for the purposes of search and/or examination
- ☐ received by this Authority as an amendment* on _____
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:
- The sequence listing in the description pages 1,2 as originally filed.

* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."